REMARKS

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Marcotte et al, *Tetrahedron Letters*, 2201, 42, 5879-5882 in view of Wong et al, Bioorganic & *Medicinal Chemistry Letters*, 1998, 8, 2333-2338. The Examiner rejects the applicant's claims as being unpatentable over Marcotte and al in view of Wong et al on the ground that:

one of ordinary skill in the art would be motivated to make the claimed compounds and their compositions since structurally similar compounds comprising the gemdifluoromethylene group directly attached to the anomeric carbon are hydrolyticallyb stable (as taught by Marcotte) and the non halogenated analogs show E-and P-selectin binding inhibition which is important for treatment for inflammation (as taught by Wong). It would be obvious to make the claimed compounds by incorporating the difluoromethylene moiety in the structure of Wong.

1/ This rejection, is respectfully traversed. Marcotte et al. does not teach specifically a sugar derivative wherein an amide group is directly attached to the gemdifluoromethylene group and also has an OGP (oxygen of the OH protected)

2/ Wong, drawn to C-glycosides, teaches sugar derivatives of structureal formula 3-8. The sugar moiety of Wong has an oxygen attached to the anomeric carbon. According to Wong these structures are useful as mimics of sialyl Lewis X as inhibitors of E and P selectins.

3/ However, Wong does not teach a derivative comprising a gemdifluoromethylene group.

- The differences raised by the Examiner in the above paragraph 1/ is taken into consideration.

- Concerning the above paragraph 2/ it should be emphasised on the fact, that in contrast to the Examiner's opinion, Wong does not teach an oxygen attached to the anomeric bound.

- The difference raised in the above paragraph 3/ is taken into consideration so that it appears that neither Marcotte nor Wong includes information that will lead a chemist skilled on the art to imagine that in addition of a lateral chain bearing a CF_2, an additional hydroxyl or protected oxygen will be important for biological activity.

- It should be also emphasised that the applicant not only uses a difluorinated atom in order to construct a hydrolytically stable compound but also adds an hydroxyl on the anomeric position to allow sugar to exist in different solutions as a classical sugar.

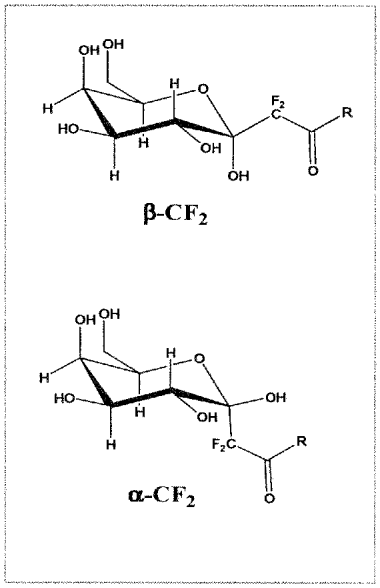
In fact Marcotte leads one to believe that the use of CF_2 glycoside can be useful as a not hydrolyable mimetic sugar in biologically active compounds. That's why the applicant's team (which is also Marcotte's team) has initially developed fluorinated sugar. However, this fact does not mean that the applicant's claimed solution can be considered by a chemist to be obvious.

Compared to Marcotte's results, which deal with the replacement of an oxygen on the anomeric position to have stable glycoderivatives, the applicant keeps the oxygen out the anomeric position to have a possible interaction with receptors such as through hydrogen bonding, as well as to retain all the properties of classical sugars (ring opening and closing) but

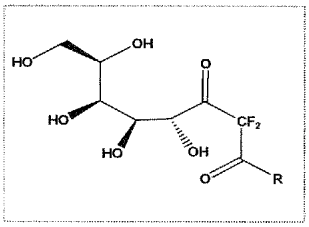
without cleaving of the lateral chain that generally occurs in this case.

It was not evident according to these really preliminary results that an hydroxyl, in addition to a CF_2 derivative, may lead to stable compounds and have utility as in biological compounds.

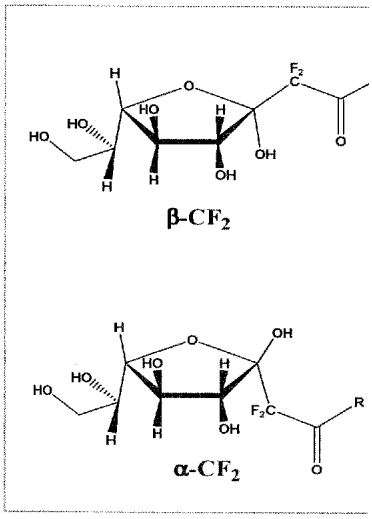
There was no way of predicting, what might be the proportion of the different forms in solution, because it was impossible to anticipate the effect of the fluorine in the opening and in the 5 or 6 membered ring cyclisation of the sugar. Indeed it is different for each type of sugar, depending on the R substituent.



Pyranoses



Linear



Furanoses

Claims 4-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lerner et al, J. Org. Chem. 1979, 441(19), 3368-3373 in combination with Furstner, Synthesis, 1989, 571-590. This rejection is respectfully traversed.

In Lerner, the reaction performed is a Reformatsky with a $BrCH_2CO_2Et$ on a 5 membered ring lactone.

The applicant reacts a 6-membered ring lactone and the reagent is $BrCF_2CO_2Et$. All the reagents are different except for the zinc. So according to the background in fluorinated chemistry and the knowledge of a chemist skilled on the art, it was not evident that the applicant's process would work.

Moreover, it would have been obvious to perform the Reformatsky with $BrCF_2CO_2Et$, on a five-membered ring lactone (of sugar). However as has been emphasized, this reaction was not expected to work in a six-membered ring as claimed herein.

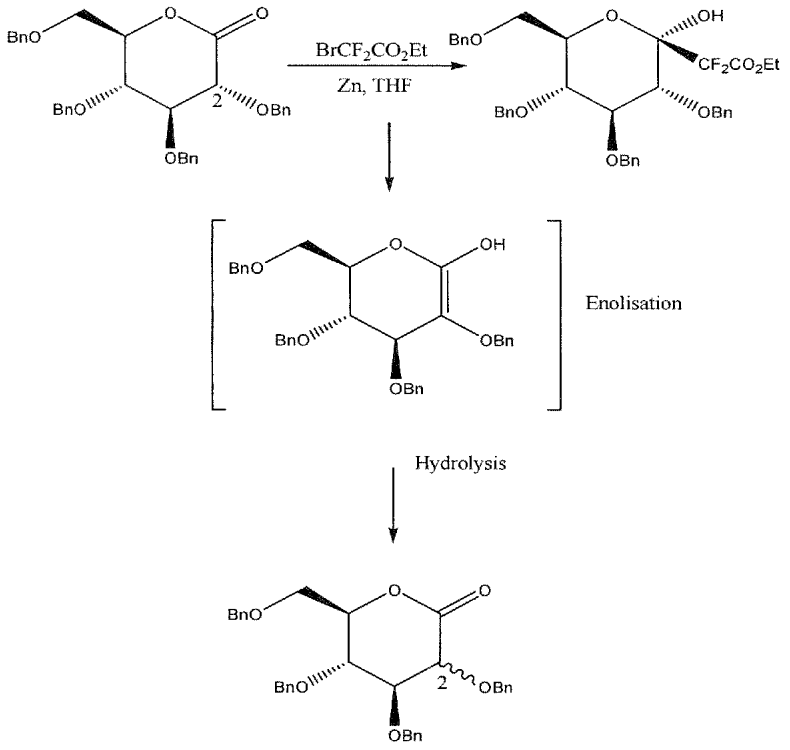
The synthesis and introduction of a fluorinated substituent was not easy to handle, particularly because, it was also done on the anomeric position of the sugar.

Furtsner's review deals with Reformatsky reaction including a part on the addition of $BrCF_2CO_2E$ onto aldehydes and ketones. There is no indication that this addition has been performed on lactones, perhaps because a chemist skilled in the art would assume that a lactone was not a good enough electrophile to undergo the addition of such a weak nucleophile as a fluorinated reagent.

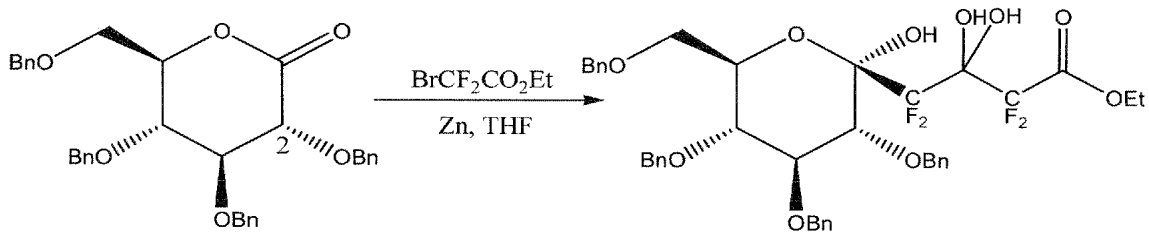
It is not obvious to apply a Reformatsky reaction of a $BrCF_2CO_2Et$ on a 6-membered ring lactone (of a carbohydrate), because such carbohydrates are often subject to elimination.

Therefore, for a chemist skilled in the art, became the $BrCF_2CO_2Et$ is not as good as a nucleophile as the $BrCH_2CO_2Et$, and will work more as a base (to abstract an enolisable

hydrogen) the enolisation will occur, with an epimerisation of the Hydrogene in position 2 of the sugar. This is more classical reaction for a chemist skilled in the art, rather than the results obtained by the applicant.

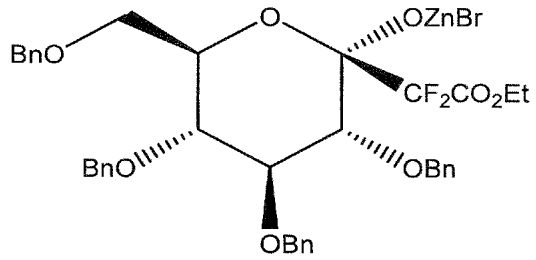


In addition, it was also obvious that the reactivity of the difluorinated ester (carbonyl is strongly activated by the fluorine atoms) is higher than the lactone (starting material), which means, that as soon as a first addition hasbeen achieved on the lactone, a second addition, of a $BrCF_2CO_2Et$, can occur on the first ester.



The only thing that prevent this from accruing is the existence of the intermediate.

The zinc derivative prevents by electronic repulsion, the addition of a second molecule of $BrCF_2CO_2Et$.



It means that the applicant has to prevent the slightest traces of protonation sources in the solvent or in atmosphere.

It has been a hard and difficult work and a lot of time to develop the chemistry to achieve these processes, and it was more obvious for a chemist skilled in the art that the Reformatsky was not a good reaction for obtaining these derivatives.

Bioorganic & Medicinal Chemistry Letters, 1998, 8, 2333-2338 (Wong et al.):

Then of course it was evident for the applicant (thanks to its background and experiences in this area), that its process can be applied to derivatives such as described in the Wong publication. But it wasn't evident for chemists that have not worked as much as the applicant in this area, i.e. for a classical chemist before the time the applicant conducted this work.

The following tests show the better effect of the applicant's compounds compared to Wong's derivatives and compared to CF_2glycoside without an additional hydroxyl on the anomeric position (comparison with Marcotte-like compounds.

These compounds have been obtained through the applicant's patented process with additional step of removal this hydroxyl):

The inhibition tests of selectins has been made in the French laboratory "Laboratoire de Pharmacologie Chimique et Génétique de Paris V (U 2666 INSERM - FRE 2463 CNRS)" according to the principle disclosed by DeFrees (DeFrees, S.; Kosch, W.; Way, W.; Paulson, J.; Sabesan, S.; Halcomb, R.; Huang, D.-H.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1995,** *117*, 66-79):[1]

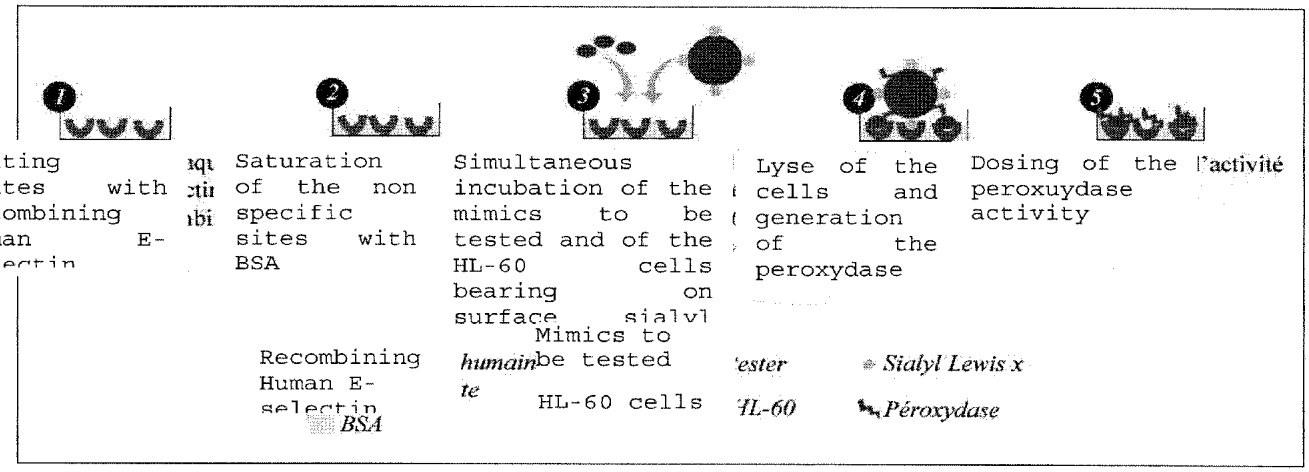
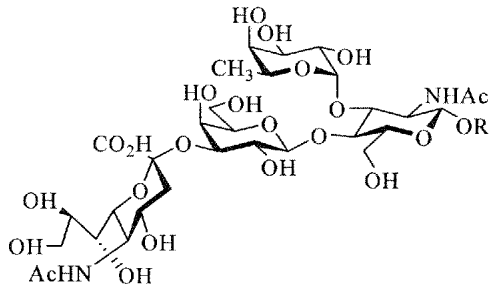


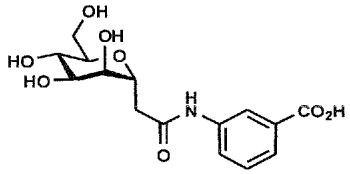
Schéma 1. Principle of the inhibition tests of selectins

The test comprises five steps. In a first step the plates containing the wells were coated with recombinant human E-selectin. Thereafter the non specific sites were saturated with Bovin Serum Albumine (BSA). A solution of HL-60 cells bearing on surface SLe^x and solutions diffently diluted with inhibitors were put in incubation on the surface of the plates. The plates were then rinced for eliminating the cells not having affinity with E-selectin. At least in order to know the potential inhibition, the cells linked to the substrate are

lysed, thus generating peroxydase which is dosed by absorbance at 492nm.



Sialyl Lewis X
E-sélectine : IC_{50} = 0,2 mM
P-sélectine : IC_{50} = 6,2 mM

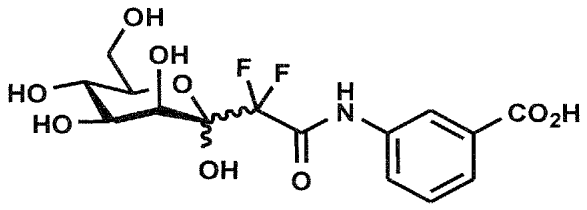


E-Selectin : IC50 = 23.6 mM
P-Selectin : IC50 > 50 mM

Results of the inhibition tests for the sialyl Lewis x and a Wong product

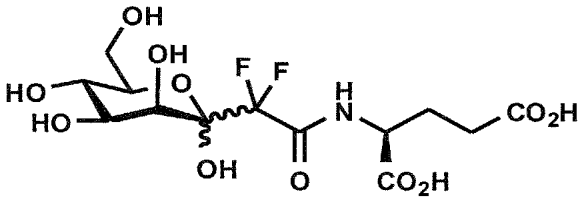
The results obtained differ from that disclosed by Wong because the test conditions are not the same. In fact Wong uses the method described by Nifant'ev[39] where the incubation is made only with a polymer of SLe^a and not with cells HL-60 the surface of which bears SLe^x.

Under the same conditions Glycosides CF_2 shows a well superior efficiency.

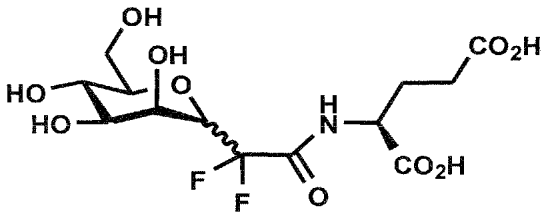


E-Selectin : IC50 = 5.1 mM
P-Selectin : IC50 = 6.8 mM

The following formulas are represented in order to compare the efficiency of the compound of the type CF_2-glycosides with or without supplemental hydroxyl:



E-Selectin : IC50 = 18.3 mM



β anomer
E : IC_{50} = 50 mM

All of these results underline the fact that the applicant's CF_2 derivatives with an additional hydroxyl bring a real improvement in term of biological activity compared to the

Wong (CH_2) derivatives, but also to Marcotte (CF_2 without OH) derivatives

For these reasons it is respectfully submitted that the applicant's invention as claimed in the claims cannot be considered as obvious and that the claims comply with the inventiveness requirements.

In view of the foregoing, early and favourable reconsideration of this office action together with the allowance of the previously amended claims is respectfully solicited.

Respectfully submitted,

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